DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 26 1999

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Sidney M. Wolfe, M.D.
Larry Sasich, Pharm.D., M.P.H.
Public Citizen's Health Research Group
1600 20th Street NW
Washington, DC 20009-1001

Re: Docket No. 98P-0622/CP1

Dear Dr. Wolfe and Dr. Sasich:

This responds to your citizen petition, dated July 29, 1998, requesting that the Food and Drug Administration (FDA) ban the sale of the drug product troglitazone on the United States market. The Agency carefully considered the issues you raised and asked the Endocrinologic and Metabolic Drugs Advisory Committee (E&MAC) to evaluate the benefits and risks of this drug. For the reasons discussed below, your citizen petition is denied.

On January 29, 1997, FDA approved the new drug application for troglitazone (brand name Rezulin) sponsored by Parke-Davis Pharmaceutical Research (Parke-Davis), a division of Warner-Lambert Company. Troglitazone is a noninsulin, orally-administered drug product for the treatment of type 2, adult-onset diabetes mellitus. After launch of the product, FDA and the sponsor received reports of liver toxicity and injury, including two cases of liver failure resulting in one death and a liver transplant. Parke-Davis added a warning to the troglitazone label and issued a "Dear Doctor" letter on October 28, 1997, notifying healthcare professionals of the hepatic adverse events, the label warning, and the recommendation to monitor serum transaminase levels of patients receiving troglitazone.

On December 1, 1997, after more reports of liver toxicity, FDA announced that patients taking troglitazone should be monitored more frequently for signs of hepatic failure. On the same day, Parke-Davis added a boxed warning to the troglitazone label and sent another "Dear Doctor" letter recommending more frequent blood testing. At the same time, Glaxo Wellcome Inc. temporarily suspended sale of its troglitazone product in the United Kingdom pending further review of safety data. On June 5, 1998, Parke-Davis announced that the National Institutes of Health (NIH) had decided to discontinue the troglitazone treatment arm of their diabetes prevention clinical trial. NIH made its decision after a patient receiving troglitazone died of acute liver failure. Parke-Davis sent another "Dear Doctor" letter on July 27, 1998, notifying health professionals of further labeling changes concerning monitoring of patients receiving troglitazone. Parke-Davis also discontinued two studies designed to test the effectiveness of troglitazone in patients with impaired glucose tolerance but not overt diabetes.

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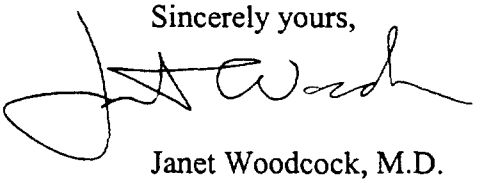
The "Dear Doctor" letters and the labeling changes recommending increased liver monitoring of patients on troglitazone were meant to decrease the incidence of hepatic toxicity and injury or failure associated with the drug. However, FDA continued to receive reports of hepatotoxicity despite the recommendations for more stringent monitoring. Therefore, the Agency decided that it was appropriate to address whether troglitazone should remain on the market and that, as part of its decision-making process, it should ask the E&MAC for advice and recommendations. See 21 CFR 14.5(a).

The E&MAC met on March 23, 1999, to review the experience with troglitazone since it was approved for marketing and to consider the benefits and risks of troglitazone in the treatment of type 2 diabetes mellitus. In addition to presentations by Parke-Davis and FDA, the committee heard a presentation by Dr. Wolfe in which he recommended that troglitazone be removed from the market. The consensus of the committee was that troglitazone should remain on the market for concomitant use with insulin or a sulfonylurea, but that the risks outweighed the benefits for troglitazone as monotherapy. The committee made a number of recommendations for revising the labeling. FDA and Parke-Davis have been working on the physician labeling and a revised version should be in use shortly. Patient labeling is also under development and will be available soon.

The agency has evaluated the recommendations of the E&MAC and has determined, given the currently known benefits and risks of troglitazone, that revising troglitazone labeling and limiting its use to concomitant use with insulin or a sulfonylurea is a reasonable and prudent action at this time. I can assure you that the agency will continue to monitor troglitazone very carefully, and will take appropriate actions as the evidence with respect to both the benefits and risks of troglitazone changes.

The Agency considers this a final response to your petition. You may submit a new petition if you believe that additional action is warranted.

Sincerely yours,



Janet Woodcock, M.D.
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